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(54) SUSTAINED-RELEASE MICROSPHERE CONTAINING ANTIPSYCHOTIC AND PROCESS FOR PRODUCING THE SAME

EIN ANTIPSYCHOTIKUM ENTHALTENDE MIKROKUGEL ZUR VERZÖGERTEN FREISETZUNG UND VERFAHREN FÜR IHRE HERSTELLUNG

MICROSPHERE A LIBERATION PROLONGEE CONTENANT UN ANTIPSHYCHOTIQUE ET PROCEDE DE PRODUCTION

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(56) References cited:
EP-A- 0 269 921
JP-A- 56 008 318
JP-A- 59 130 211
JP-A- 63 122 620

- **CHEMICAL ABSTRACTS, vol. 117, no. 24, 14 December 1992 Columbus, Ohio, US; abstract no. 239653, XP002009017 & J. MICROENCAPSULATION, vol. 9, no. 4, 1992, pages 415-423, Z. RAMTOOLA ET AL.: "RELEASE KINETICS OF FLUPHENAZINE FROM BIODEGRADABLE MICROSPHERES"**
- **CHEMICAL ABSTRACTS, vol. 102, no. 18, 6 May 1985 Columbus, Ohio, US; abstract no. 154676, XP002009018 & J. PHARM. SCI., vol. 74, no. 1, 1985, pages 21-24, K. SUZUKI ET AL.: "MICROENCAPSULATION AND DISSOLUTION PROPERTIES OF A NEUROLEPTIC IN A BIODEGRADABLE POLYMER,POLY (D,L-LACTIDE)"**
- **CHEMICAL ABSTRACTS, vol. 106, no. 6, 9 February 1987 Columbus, Ohio, US; abstract no. 38375, XP002009019 & DRUG DEV. IND. PHARM., vol. 12, no. 14, 1986, pages 2355-2380, R. K. CHANG ET AL.: "DISSOLUTION CHARACTERISTICS OF POLYCAPROLACTONE-POLYLACTIDE MICROSPHERES OF CHLORPROMAZINE"**

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The file contains technical information submitted after the application was filed and not included in this specification

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Description

[0001] This invention relates to a sustained release microsphere preparation which contains a hydrophobic antipsychotic drug and to a production process thereof.

Background Art

[0002] It is said that, in the drug therapy of mental diseases, maintenance therapy by continuous administration is effective in preventing recidivation of symptoms whereby it has come to be possible to guide patients in their daily life. However, since the current maintenance therapy with antipsychotic drugs is carried out by orally administering tablets or fine granules once a day or dividing the daily dose into several doses per day, decreased compliance during the maintenance therapy becomes a cause of recidivation of symptoms or re-hospitalization. Consequently, it has a drawback in that certain means must be employed to improve compliance after rehabilitation or during outpatient maintenance therapy.

[0003] In order to resolve this problem, long acting injections containing drugs in the form of decanoic acid ester or enanthic acid ester have been used. For example, decanoic acid esters of haloperidol and bromperidol are disclosed in JP-A-56-8318 (the term "JP-A" as used herein means "unexamined published Japanese Patent Application"), and decanoic acid ester or enanthic acid ester of fluphenazine is also known and used in the therapeutic field.

[0004] However, these prior long acting injections have drawbacks in that their administration route is limited to intramuscular injection, resistance at the time of administration is large because they are oil injections while the dispersibility of oil in muscular is small, and their administration gives patients severe pain. In addition, there is a possibility that their effects may vary depending on individuals and ages because, though the ester bodies of active ingredients show a sustained release effect in the living body by gradually releasing their active bodies due to the influence of esterase, release of drugs in the living body generally depends on their transition rate from the administered part into lymphoid system and also on the enzyme activity. Accordingly, it has been demanded to develop new long acting injections in which original drugs themselves are used.

[0005] On the other hand, each of JP-A-62-201816, JP-B-1-57087 and JP-B-2-124814 (the term "JP-B" as used herein means "examined Japanese Patent Publication") discloses sustained release microcapsules which make possible to administrate water soluble drugs at an interval of once a week or a month and production processes thereof. Also, JP-A-55-33414 and EP-A-0 269 921 disclose a so-called in-water drying method in which a hydrophobic drug and polylactic acid are dissolved in a common organic solvent, the resulting solution is emulsified by adding a phase separation agent and then the solvent is removed by evaporation to obtain fine particles.

Disclosure of the Invention

[0006] With the aim of improvement in compliance at the time of maintenance therapy with hydrophobic antipsychotic drugs, the present inventors have conducted intensive studies on the development of a sustained release pharmaceutical preparation in which a drug itself is used as an active ingredient without modification. As the result, it was found that a drug can be released at an almost constant rate extending over 1 week or more by including a hydrophobic antipsychotic drug into a base comprising a biodegradable high molecular weight polymer having *in vivo* histocompatibility to make a sustained release microsphere preparation and administrating it by subcutaneous or intramuscular injection, hence resulting in the accomplishment of the present invention.

[0007] Accordingly, the present invention relates to (1) an antipsychotic drug-containing sustained release microsphere preparation which is produced by including a hydrophobic antipsychotic drug in the form of microcrystals having an average particle size of 5 μm or less into a base comprising a high molecular weight polymer having *in vivo* histocompatibility and (2) a process for producing an antipsychotic drug-containing sustained release microsphere preparation which comprises making an oil layer comprising a solution of a high molecular weight polymer having *in vivo* histocompatibility containing a hydrophobic antipsychotic drug, adding the oil layer to a water layer, subjecting the resulting mixture to an emulsification treatment to obtain an O/W type emulsion and subsequently removing the solvent in the oil layer by in-water drying method.

[0008] The hydrophobic antipsychotic drug to be applied to the present invention is selected from haloperidol, bromperidol, fluphenazine, chlorpromazine, sulpiride, carpipramine, clocapramine, mosapramine, risperidone, clozapine, oranzapine and sertindole and pharmaceutically acceptable acid addition salts thereof, preferably from the group consisting of haloperidol, bromperidol, fluphenazine maleate, chlorpromazine, chlorpromazine hibenzoate, sulpiride, carpipramine hydrochloride, carpipramine maleate, clocapramine hydrochloride, mosapramine hydrochloride, risperidone, clozapine, oranzapine and sertindole, of which haloperidol or bromperidol is particularly preferred.

[0009] The base that constitutes the sustained release microspheres of the present invention should have such a function that its concentration in blood plasma can be maintained at a constant level by a single administration whereby its effects can be obtained stably over a prolonged period of time. A biodegradable high molecular weight polymer having *in vivo* histocompatibility is used as a base having such a function. The sustained

release microspheres of the present invention are constructed in the manner that the hydrophobic antipsychotic drug is included therein. Examples of such a high molecular weight polymer having *in vivo* histocompatibility include polymers of fatty acid esters or copolymers thereof, polyacrylic esters, polyhydroxybutyric acids, polyalkylene oxalates, polyorthoester, polycarbonate and polyamino acids, which may be used alone or as a mixture of two or more. Illustrative examples of the polymers of fatty acid esters or copolymers thereof include polylactic acid, polyglycolic acid, polycitric acid, polymalic acid and poly(lactic-co-glycolic)acid, which may also be used alone or as a mixture of two or more. Another useful examples include poly-α-cyanoacrylic ester, poly-β-hydroxybutyric acid, polytrimethylene oxalate, polyorthoester, polyorthocarbonate, polyethylene carbonate, poly γ-benzyl-L-glutamic acid and poly L-alanine, which may be used alone or as a mixture of two or more. Of these polymers, polylactic acid, polyglycolic acid or poly(lactic-co-glycolic)acid may be used preferably.

[0010] These *in vivo* histocompatible high molecular weight polymers to be used in the present invention may have an average molecular weight of preferably from about 2,000 to about 80,000, more preferably from about 5,000 to about 20,000. When poly(lactic-co-glycolic)acid is used as the *in vivo* histocompatible high molecular weight polymer, compositional ratio of lactic acid and glycolic acid may be in the range of from about 100:0 to 50:50, preferably at 75:25 and 50:50.

[0011] Although the amount of the high molecular weight polymer(s) is decided by the drug-releasing rate, period and the like, and may be controlled within in a range of from about 0.2 to about 10,000 times by weight of the drug, it is preferred that the high molecular weight polymer is used as the base of the microsphere preparation of the present invention in an amount of from 1 to 1,000 times by weight of the drug.

[0012] A solution containing the above high molecular weight polymer (oil layer) is prepared by dissolving the high molecular weight polymer in a solvent. The concentration of the high molecular weight polymer in the oil layer may be in the range of preferably from about 0.5 to about 90% (w/w), more preferably from about 2 to about 60% (w/w).

[0013] Examples of the solvent include those which have a boiling point of about 120°C or lower, do not show miscibility with water and can dissolve high molecular weight polymers, such as alkane halides (dichloromethane, chloroform, chloroethane, dichloroethane, trichloroethane and the like), ethyl acetate, ethyl ether, cyclohexane, benzene, n-hexane, toluene and the like, which may be used alone or as a mixture of two or more.

[0014] In the production process of the microsphere preparation, a hydrophobic antipsychotic drug is dispersed in a solution prepared by dissolving a *in vivo* histocompatible high molecular weight polymer in a solvent to give an oil layer. The thus obtained oil layer is added to a water layer and subjected to an emulsification treatment to prepare an O/W type emulsion. Thereafter, the microsphere preparation is obtained by removing the solvent in the oil layer by means of in-water drying method.

[0015] When the oil layer is prepared by dispersing a drug, the drug may be used after making it into fine particles. By the use of microcrystals, the surface of microspheres becomes smooth and the drug release becomes close to 0 order. Such a releasing capacity close to 0 order seems to be accomplished due to decrease in the initial releasing rate resulting from the increased interaction between the afore-mentioned high molecular weight polymer and the drug effected by the increased contacting area and due to increase in the releasing rate in the late stage effected by the increased surface area of the drug. The finely ground drug have a particle size of 5 μm or less (about 0.1 to about 5 μm, preferably 0.5 to 5 μm). Fine particles of the drug can be obtained by usually used means. Examples of such means include jet mill, ball mill, vibrating mill, hammer mill, colloid mill and the like.

[0016] In preparing microspheres of the present invention, it is preferable to add an emulsifying agent to the water layer, and examples thereof include those which are able to form a stable O/W type emulsion, such as an anionic surfactant (sodium oleate, sodium stearate, sodium lauryl sulfate or the like), a nonionic surfactant (a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene castor oil derivative or the like), polyvinyl pyrrolidone, polyvinyl alcohol, carboxymethylcellulose, lecithin, gelatin and the like, which may be used alone or as a mixture of two or more. These agents may be used in a concentration of from about 0.01% to about 20%, more preferably from about 0.05% to about 10%.

[0017] Removal of the solvent from the oil layer is effected by a conventionally used means (in-water drying method: Tamotsu Kondo, "Maikurokapuseru-sono kinou to ouyou (Microcapsules, Their Functions And Applications)", p.78, Japanese Standards Association, March 20, 1991). In this method, a solvent is removed by gradually reducing pressure while stirring using a propeller mixer, a magnetic stirrer or the like or by controlling the degree of vacuum using a rotary evaporator or the like.

[0018] The thus obtained microspheres are collected by centrifugation or filtration, washed several times with distilled water to remove free drug, the emulsifying agent and the like adhered to the surface of the microspheres and then treated under a reduced pressure, if necessary, with heating, to perfect removal of water and solvent in the microspheres.

[0019] If necessary, the thus obtained microspheres are gently ground and screened to remove oversized microspheres. When used as suspensions for injection use, the particle size of the microspheres may be a range which can satisfy their dispersibility and needle-passing property, for example, in the range of from

about 0.5 to about 400 μm, more preferably from about 0.5 to about 200 μm, as an average particle size.

[0020] The microspheres of the present invention can be made into sustained release injections by preparing an aqueous suspension together with a dispersing agent (polysorbate 80, sodium carboxymethylcellulose, sodium alginate or the like), a preservative (methylparaben, propylparaben, benzyl alcohol, chlorobutanol or the like) and an isotonic agent (sodium chloride, glycerol, sorbitol, glucose or the like) or by preparing an oily suspension by dispersing the microspheres in a plant oil such as olive oil, sesame oil, peanut oil, cotton oil, corn oil or the like or in propylene glycol or the like. In this instance, in order to lessen resisting feeling at the time of injection, the sustained release microsphere preparation of the present invention may be used preferably in the form of aqueous suspension.

[0021] In addition, sustained release injections of microspheres of the present invention can be made into more stable sustained release injections by further mixing the above composition with a filler (mannitol, sorbitol, lactose, glucose or the like), dispersing the mixture and then subjecting the resulting dispersion to freeze drying or spray drying to obtain a solid preparation which is used by adding distilled water for injection use or an appropriate dispersion medium at the time of injection.

[0022] Dose of a hydrophobic antipsychotic drug as the active ingredient of the sustained release microsphere preparation of the present invention can be decided depending on each disease to be treated, symptoms and age of each patient and the like, and it may be in the range of generally from 5 to 5,000 mg, preferably from 10 to 2,000 mg, per adult per administration. Since the pharmaceutical preparation of the present invention releases its active ingredient depending on the hydrolysis of the high molecular weight polymer by water, it shows less individual difference and can be administered by not only intramuscular injection but also subcutaneous injection.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023]

Fig. 1 is a graph showing remaining amount of bromperidol in the administered area of rat after intramuscular injection of each of the microsphere preparations obtained in Examples 1 to 3.

Fig. 2 is a graph showing periodical changes in the drug concentration in blood plasma of rat after intramuscular injection of the haloperidol-containing microsphere preparation obtained in Example 4.

Fig. 3 is a graph showing results of an *in vitro* drug release test of the microsphere preparation obtained in Test Example 3.

BEST MODE OF CARRYING OUT THE INVENTION

[0024] The following Examples and Test Examples are provided to illustrate the present invention further in detail.

EXAMPLE 1 (not part of the claimed invention)

[0025] Poly(lactic-co-glycolic)acid (50:50) (molecular weight: about 20,000) was dissolved in 3 ml of dichloromethane to prepare a 40% solution. In this was dissolved 190 mg of bromperidol (average particle size: 13.0 μm) to prepare a mixed solution. This was poured into 1,000 ml of 0.5% polyvinyl alcohol (Gosenol EG-40, manufactured by The Nippon Synthetic Chemical Industry) and dispersed using a homogenizer (manufactured by Tokushu Kika Kogyo) to prepare an O/W type emulsion. Thereafter, the O/W type emulsion was gently stirred using a conventional mixer to effect evaporation of dichloromethane and solidification of microspheres which were subsequently collected by centrifugation, simultaneously washing with distilled water. The thus recovered microspheres were made into a powder preparation by freeze drying.

EXAMPLE 2

[0026] *dl*-Polylactic acid (molecular weight: about 10,000) was dissolved in 3 ml of dichloromethane to prepare a 20% solution. In this was suspended 190 mg of bromperidol (average particle size: 2.5 μm) to obtain a mixed solution. Thereafter, a bromperidol-containing microsphere preparation was obtained in the same manner as described in Example 1.

EXAMPLE 3 (not part of the claimed invention)

[0027] *dl*-Polylactic acid (molecular weight: about 20,000) was dissolved in 3 ml of dichloromethane to prepare a 20% solution. In this was dissolved 85 mg of bromperidol (average particle size, 13.0 μm) to obtain a mixed solution. Thereafter, a bromperidol-containing microsphere preparation was obtained in the same manner as described in Inventive Example 1.

EXAMPLE 4

[0028] *dl*-Polylactic acid (molecular weight, about 10,000) was dissolved in 4 ml of dichloromethane to prepare a 30% solution. In this was suspended 380 mg of haloperidol (average particle size: 3.0 μm) to obtain a mixed solution. Thereafter, a haloperidol-containing microsphere preparation was obtained in the same manner as described in Example 1.

EXAMPLE 5

[0029] A microsphere preparation is obtained in the

same manner as described in the above Examples using fluphenazine maleate, chlorpromazine, chlorpromazine hibenzoate, sulpiride, carpipramine hydrochloride, carpipramine maleate, clocapramine hydrochloride, mosapramine hydrochloride, risperidone, clozapine, oranzapine or sertindole as the drug.

TEST EXAMPLE 1

[0030] Each of the bromperidol-containing microsphere preparations obtained in Examples 1 to 3 was suspended in physiological saline and administered into the femoral muscle of male SD rats (15 weeks of age) in a dose of 12.5 mg as bromperidol. After a predetermined period of time, microspheres remained in the administered area were periodically recovered to measure remaining amount of bromperidol. As the result, release of the drug at an almost constant rate was confirmed as shown in Fig. 1.

TEST EXAMPLE 2

[0031] The haloperidol-containing microsphere preparation obtained in Example 4 was suspended in a 0.5% sodium carboxymethylcellulose solution isotonized with mannitol and administered into the femoral muscle of male SD rats (13 weeks of age) in a dose of 25 mg as haloperidol. After a predetermined period of time, blood samples were periodically collected from ophthalmic veins to measure concentration of the drug in blood plasma. As the result, sustained concentration of haloperidol in blood plasma was confirmed as shown in Fig. 2.

TEST EXAMPLE 3

[0032] A 25 mg portion of each of the bromperidol-containing microsphere preparations obtained from the following formulations A and B was dispersed in 20 ml of physiological saline and shaken at 37°C and at 80 revolutions per minute using a constant temperature shaker (manufactured by Yamato Kagaku). Thereafter, samples were periodically collected to calculate drug releasing ratio by ultraviolet absorption photometry (245 nm). As shown in Fig. 3, it was confirmed that the microsphere preparation of formulation A which comprises finely ground bromperidol can release the drug at a rate of almost 0 order.

FORMULATION A

[0033] *dl*-Polylactic acid (molecular weight: about 5,000) was dissolved in 3 ml of dichloromethane to prepare a 12% solution. In this was suspended 190 mg of bromperidol (average particle size: 2.5 μm) to obtain a mixed solution. Thereafter, a bromperidol-containing microsphere preparation was obtained in the same manner as described in Example 1.

FORMULATION B

[0034] Bromperidol with no grinding (average particle size: 13.0 μm) was used in stead of the bromperidol of Formulation A having an average particle size of 2.5 μm.

INDUSTRIAL APPLICABILITY

[0035] According to the hydrophobic antipsychotic drug-containing sustained release microsphere preparation of the present invention, considerable improvement in compliance in maintenance therapy of mentally deranged persons can be expected because of the following features of the preparation of the present invention.

(1) When a long-term administration is required, desired pharmacological effects can be obtained continuously by one injection per 1 to 8 weeks, in stead of daily administration.
(2) Since a biodegradable high molecular weight polymer is used, surgical operations such as embedding and the like are not required at all, and subcutaneous and intramuscular administrations can be made easily absolutely in the same manner as the case of conventional suspension injections so that recovery of the material is not required.
(3) Pain and resistance at the time of administration are small.

Claims

1. An antipsychotic drug-containing sustained release microsphere preparation which is produced by including a hydrophobic antipsychotic drug in the form of microcrystals having an average particle size of 5 μm or less into a base comprising a high molecular weight polymer having *in vivo* histocompatibility.

2. The antipsychotic drug-containing sustained release microsphere preparation according to claim 1 wherein said hydrophobic antipsychotic drug is selected from haloperidol, bromperidol, fluphenazine, chlorpromazine, sulpiride, carpipramine, clocapramine, mosapramine, risperidone, clozapine, oranzapine and sertindole and pharmaceutically acceptable acid addition salts thereof.

3. The antipsychotic drug-containing sustained release microsphere preparation according to claim 1 or 2, wherein said hydrophobic antipsychotic drug is selected from haloperidol, bromperidol, fluphenazine maleate, chlorpromazine, chlorpromazine hibenzoate, sulpiride, carpipramine hydrochloride, carpipramine maleate, clocapramine hydrochloride, mosapramine hydrochloride, risperidone, clozap-

ine, oranzapine and sertindole.

4. The antipsychotic drug-containing sustained release microsphere preparation according to claim 1, wherein said hydrophobic antipsychotic drug is selected from haloperidol and bromperidol.

5. The antipsychotic drug-containing sustained release microsphere preparation according to claim 1, wherein said high molecular weight polymer having *in vivo* histocompatibility is one or more compounds selected from polymers of fatty acid esters or copolymers thereof, polyacrylic esters, polyhydroxybutyric acids, polyalkylene oxalates, polyorthoester, polycarbonate and polyamino acids.

6. The antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 1 to 5, wherein said high molecular weight polymer having *in vivo* histocompatibility is one or more compounds selected from polylactic acid, polyglycolic acid, polycitric acid, polymalic acid and poly(lactic-co-glycolic)acid.

7. The antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 1 to 6, wherein said high molecular weight polymer having *in vivo* histocompatibility is one or more compounds selected from polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, poly(lactic-co-glycoli)acid, poly-α-cyanoacrylic ester, poly-β-hydroxybutyric acid, polytrimethylene oxalate, polyorthoester, polyorthocarbonate, polyethylene carbonate, poly-γ-benzyl-L-glutamic acid and poly-L-alanine.

8. The antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 1 to 7, wherein said hydrophobic antipsychotic drug is in the form of microcrystals having an average particle size of from 0.1 to 5 μm.

9. The antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 1 to 8, wherein said antipsychotic drug-containing sustained release microsphere preparation is an aqueous suspension.

10. A process for producing an antipsychotic drug-containing sustained release microsphere preparation which comprises making an oil layer comprising a high molecular weight polymer having *in vivo* histocompatibility containing a hydrophobic antipsychotic drug in the form of microcrystals having an average particle size of 5 μm or less, adding the oil layer to a water layer, subjecting the resulting mixture to an emulsification treatment to obtain an O/W type emulsion and subsequently removing the solvent in the oil layer by in-water drying method.

11. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to claim 10, wherein said hydrophobic antipsychotic drug is selected from haloperidol, bromperidol, fluphenazine, chlorpromazine, sulpiride, carpipramine, clocapramine, mosapramine, risperidone, clozapine, oranzapine and sertindole and pharmaceutically acceptable acid addition salts thereof.

12. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to claim 10 or 11, wherein said hydrophobic antipsychotic drug is selected from haloperidol, bromperidol, fluphenazine maleate, chlorpromazine, chlorpromazine hibenzoate, sulpiride, carpipramine hydrochloride, carpipramine maleate, clocapramine hydrochloride, mosapramine hydrochloride, risperidone, clozapine, oranzapine and sertindole.

13. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to claim 10, wherein said hydrophobic antipsychotic drug is selected from haloperidol and bromperidol.

14. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to claim 10, wherein said high molecular weight polymer having *in vivo* histocompatibility is one or more compounds selected from polymers of fatty acid esters or copolymers thereof, polyacrylic esters, polyhydroxybutyric acids, polyalkylene oxalates, polyorthoester, polycarbonate and polyamino acids.

15. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 10 to 14, wherein said high molecular weight polymer having *in vivo* histocompatibility is one or more compounds selected from polylactic acid, polyglycolic acid, polycitric acid, polymalic acid and poly(lactic-co-glycolic)acid.

16. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 10 to 15, wherein said high molecular weight polymer having *in vivo* histocompatibility is one or more compounds selected from polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, poly(lactic-co-glycolic)acid, poly-α-cyanoacrylic ester, poly-β-hydroxybutyric acid, polytrimethylene oxalate, polyorthoester, polyorthocarbonate, polyethylene car-

bonate, poly-γ-benzyl-L-glutamic acid and poly-L-alanine.

17. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 10 to 16, wherein said hydrophobic antipsychotic drug is in the form of microcrystals having an average particle size of from 0.1 to 5 μm.

18. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 10 to 17, wherein a solvent of said solution of high molecular weight polymer having *in vivo* histocompatibility is a solvent which has a boiling point of 120°C or less and does not admix with water.

19. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 10 to 18, wherein one or more compounds selected from anionic surfactants, nonionic surfactants, polyvinyl pyrrolidone, polyvinyl alcohol, carboxymethylcellulose, lecithin and gelatin are added as emulsifying agents to said water layer.

20. The process for producing an antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 10 to 19, wherein said antipsychotic drug-containing sustained release microsphere preparation is an aqueous suspension.

21. The antipsychotic drug-containing sustained release microsphere preparation according to any one of claims 1 to 7, wherein said hydrophobic antipsychotic drug is in the form of microcrystals having an average particle size of from 0.5 to 5 μm.

22. A bromperidol or haloperidol-containing sustained release microsphere preparation which is produced by including bromperidol or haloperidol in the form of microcrystals having an average particle size of from 0.5 to 5 μm into a base comprising a high molecular weight polymer having *in vivo* histocompatibility.

Patentansprüche

1. Ein Antipsychotikum enthaltendes Mikrokapsel-Depotpräparat, hergestellt durch Einbringen eines hydrophoben Ahtipsychotikums in Form von Mikrokristallen mit einer mittleren Teilchengröße von 5 μm oder weniger in eine Basis, die ein Polymer mit hohem Molekulargewicht mit in vivo-Histokompatibilität umfaßt.

2. Antipsychotikum-enthaltendes Mikrokapsel-Depotpräparat nach Anspruch 1, dadurch gekennzeichnet, daß das hydrophobe Antipsychotikum ausgewählt ist aus Haloperidol, Bromperidol, Fluphenazin, Chlorpromazin, Sulpirid, Carpipramin, Clocapramin, Mosapramin, Risperidon, Clozapin, Oranzapin und Sertindol, und pharmazeutisch annehmbaren Säureadditionsalzen davon.

3. Antipsychotikum-enthaltendes Mikrokapsel-Depotpräparat nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß das hydrophobe Antipsychotikum ausgewählt ist aus Haloperidol, Bromperidol, Fluphenazin-maleat, Chlorpromazin, Chlorpromazin-dibenzoat, Sulpirid, Carpipramin-hydrochlorid, Carpipramin-maleat, Clocapramin-hydrochlorid, Mosapramin-hydrochlorid, Risperidon, Clozapin, Oranzapin und Sertindol.

4. Antipsychotikum-enthaltendes Mikrokapsel-Depotpräparat nach Anspruch 1, dadurch gekennzeichnet, daß das hydrophobe Antipsychotikum ausgewählt ist aus Haloperidol und Bromperidol.

5. Antipsychotikum-enthaltendes Mikrokapsel-Depotpräparat nach Anspruch 1, dadurch gekennzeichnet, daß das Polymer mit hohem Molekulargewicht und mit in vivo-Histokompatibilität aus einer oder mehreren Verbindungen besteht ausgewählt aus Polymeren von Fettsäurenestern oder Copolymeren davon, Polyacrylsäureestern, Polyhydroxybuttersäuren, Polyalkylenoxalaten, Polyorthoester, Polycarbonat und Polyaminosäuren.

6. Antipsychotikum-enthaltendes Mikrokapsel-Depotpräparat nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß das Polymer mit hohem Molekulargewicht und mit in vivo-Histokompatibilität aus einer oder mehreren Verbindungen besteht ausgewählt aus Polymilchsäure, Polyglykolsäure, Polycitronensäure, Polyäpfelsäure, und Poly(milchco-glykol)säure.

7. Antipsychotikum-enthaltendes Mikrokapsel-Depotpräparat nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß das Polymer mit hohem Molekulargewicht und mit in vivo-Histokompatibilität aus einer oder mehreren Verbindungen besteht ausgewählt aus Polymilchsäure, Polyglykolsäure, Polycitronensäure, Polyäpfelsäure, Poly(milch-co-glykol)säure, Poly-α-cyanoacrylester, Poly-β-hydroxybuttersäure, Polytrimethylenoxalat, Polyorthoester, Polyorthocarbonat, Polyethylencarbonat, Poly-γ-benzyl-L-glutaminsäure und Poly-L-alanin.

8. Antipsychotikum-enthaltendes Mikrokapsel-Depot-

präparat nach einem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß das hydrophobe Antipsychotikum in Form von Mikrokristallen mit einer mittleren Teilchengröße von 0,1 bis 5 µm vorliegt.

9. Antipsychotikum-enthaltendes Mikrokapsel-Depotpräparat nach einem der Ansprüche 1 bis 8, dadurch gekennzeichnet, daß das Antipsychotikum-enthaltende Mikrokapsel-Depotpräparat eine wässerige Suspension ist.

10. Verfahren zur Herstellung eines Antipsychotikum-enthaltenden Mikrokapsel-Depotpräparats umfassend die Stufen: Herstellen einer Ölschicht, die ein Polymer mit hohem Molekulargewicht und in vivo-Histokompatibilität umfaßt, und ein hydrophobes Antipsychotikum in Form von Mikrokristallen mit einer mittleren Teilchengröße von 5 µm oder weniger enthält, Zugeben der Ölschicht zu einer Wasserschicht, Unterwerfen der resultierenden Mischung einer Emulgierbehandlung, um eine O/W-Typ-Emulsion zu halten, und nachfolgendes Entfernen des Lösungsmittels in der Ölschicht mittels einer in-Wasser-Trockenmethode.

11. Verfahren zur Herstellung eines Antipsychotikum-enthaltenden Mikrokapsel-Depotpräparats nach Anspruch 10, dadurch gekennzeichnet, daß das hydrophobe Antipsychotikum ausgewählt ist aus Haloperidol, Bromperidol, Fluphenazin, Chlorpromazin, Sulpirid, Carpipramin, Clocapramin, Mosapramin, Risperidon, Clozapin, Oranzapin und Sertindol, und pharmazeutisch annehmbaren Säureadditionsalzen davon.

12. Verfahren zur Herstellung eines Antipsychotikum-enthaltenden Mikrokapsel-Depotpräparats nach Anspruch 10 oder 11, dadurch gekennzeichnet, daß das hydrophobe Antipsychotikum ausgewählt ist aus Haloperidol, Bromperidol, Fluphenazin-maleat, Chlorpromazin, Chlorpromazindibenzoat, Sulpirid, Carpipramin-hydrochlorid, Carpipramin-maleat, Clocapramin-hydrochlorid, Mosapramin-hydrochlorid, Risperidon, Clozapin, Oranzapin und Sertindol.

13. Verfahren zur Herstellung eines Antipsychotikum-enthaltenden Mikrokapsel-Depotpräparats nach Anspruch 10, dadurch gekennzeichnet, daß das hydrophobe Antipsychotikum ausgewählt ist aus Haloperidol und Bromperidol.

14. Verfahren zur Herstellung eines Antipsychotikum-enthaltenden Mikrokapsel-Depotpräparats nach Anspruch 10, dadurch gekennzeichnet, daß das Polymer mit hohem Molekulargewicht und mit in vivo-Histokompatibilität aus einer oder mehreren Verbindungen besteht ausgewählt aus Polymeren von Fettsäureestern oder Copolymeren davon, Polyacrylsäureestern, Polyhydroxybuttersäuren, Polyalkylenoxalaten, Polyorthoester, Polycarbonat und Polyaminosäuren.

15. Verfahren zur Herstellung eines Antipsychotikum-enthaltenden Mikrokapsel-Depotpräparats nach einem der Ansprüche 10 bis 14, dadurch gekennzeichnet, daß das Polymer mit hohem Molekulargewicht und mit in vivo-Histokompatibilität aus einer oder mehreren Verbindungen besteht ausgewählt aus Polymilchsäure, Polyglykolsäure, Polycitronensäure, Polyäpfelsäure und Poly(milch-co-glykol)säure.

16. Verfahren zur Herstellung eines Antipsychotikum-enthaltenden Mikrokapsel-Depotpräparats nach einem der Ansprüche 10 bis 15, dadurch gekennzeichnet, daß das Polymer mit hohem Molekulargewicht und mit in vivo-Histokompatibilität aus einer oder mehreren Verbindungen besteht ausgewählt aus Polymilchsäure, Polyglykolsäure, Polycitronensäure, Polyäpfelsäure, Poly(milch-co-glykol)säure, Poly-α-cyanoacrylester, Poly-β-hydroxybuttersäure, Polytrimethylenoxalat, Polyorthoester, Polyorthocarbonat, Polyethylencarbonat, Poly-γ-benzyl-L-glutaminsäure und Poly-L-alanin.

17. Verfahren zur Herstellung eines Antipsychotikum-enthaltenden Mikrokapsel-Depotpräparats nach einem der Ansprüche 10 bis 16, dadurch gekennzeichnet, daß das hydrophobe Antipsychotikum in Form von Mikrokristallen mit einem mittleren Teilchengröße von 0,1 bis 5 µm vorliegt.

18. Verfahren zur Herstellung eines Antipsychotikum-enthaltenden Mikrokapsel-Depotpräparats nach einem der Ansprüche 10 bis 17, dadurch gekennzeichnet, daß das Lösungsmittel der Lösung des Polymers mit hohem Molekulargewicht und in vivo-Histokompatibilität ein Lösungsmittel ist, das einen Siedepunkt von 120 °C oder weniger besitzt und sich nicht mit Wasser mischt.

19. Verfahren zur Herstellung eines Antipsychotikum-enthaltenden Mikrokapsel-Depotpräparats nach einem der Ansprüche 10 bis 18, dadurch gekennzeichnet, daß als Emulgiermittel zur Wasserschicht eine oder mehrere Verbindungen zugegeben werden ausgewählt aus anionischen oberflächenaktiven Mitteln, nichtionischen oberflächenaktiven Mitteln, Polyvinylpyrrolidon, Polyvinylalkohol, Carboxymethylcellulose, Lecithin und Gelatine.

20. Verfahren zur Herstellung eines Antipsychotikum-enthaltenden Mikrokapsel-Depotpräparats nach einem der Ansprüche 10 bis 19, dadurch gekenn-

zeichnet, daß das Antipsychotikum-enthaltende Mikrokapsel-Depotpräparat eine wässerige Suspension ist.

21. Antipsychotikum-enthaltendes Mikrokapsel-Depotpräparats nach einem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß das hydrophobe Antipsychotikum in Form von Mikrokristallen mit einer mittleren Teilchengröße von 0,5 bis 5 µm vorliegt.

22. Bromperidol- oder Haloperidol-enthaltendes Mikrokapsel-Depotpräparat, hergestellt durch Einbringen von Bromperidol oder Haloperidol in Form von Mikrokristallen mit einer mittleren Teilchengröße von 0,5 bis 5 µm in eine Basis, die ein Polymer mit hohem Molekulargewicht und mit in vivo-Histokompatibilität umfaßt.

Revendications

1. Préparation de microsphères à libération prolongée, contenant un médicament antipsychotique, qui est produite en incorporant un médicament antipsychotique hydrophobe sous forme de microcristaux ayant des dimensions moyennes de particules égales ou inférieures à 5 µm à une substance de base comprenant un polymère de haut poids moléculaire doué d'histocompatibilité in vivo.

2. Préparation de microsphères à libération prolongée contenant un médicament antipsychotique suivant la revendication 1, dans laquelle ledit médicament antipsychotique hydrophobe est choisi entre l'halopéridol, le brompéridol, la fluphénazine, la chlorpromazine, le sulpiride, la carpipramine, la clocapramine, la mosapramine, la rispéridone, la clozapine, l'oranzapine et le sertindole ainsi que leurs sels d'addition d'acides pharmaceutiquement acceptables.

3. Préparation de microsphères à libération prolongée contenant un médicament antipsychotique suivant la revendication 1 ou 2, dans laquelle ledit médicament antipsychotique hydrophobe est choisi entre l'halopéridol, le brompéridol, le maléate de fluphénazine, la chlorpromazine, le dibenzoate de chlorpromazine, le sulpiride, le chlorhydrate de carpipramine, le maléate de carpipramine, le chlorhydrate de clocapramine, le chlorhydrate de mosapramine, la rispéridone, la clozapine, l'oranzapine et le sertindole.

4. Préparation de microsphères à libération prolongée contenant un médicament antipsychotique suivant la revendication 1, dans laquelle ledit médicament antipsychotique hydrophobe est choisi entre l'halopéridol et le brompéridol.

5. Préparation de microsphères à libération prolongée contenant un médicament antipsychotique suivant la revendication 1, dans laquelle le polymère de haut poids moléculaire doué d'histocompatibilité in vivo consiste en un ou plusieurs composés choisis parmi des polymères d'esters d'acides gras ou leurs copolymères ; des polymères d'ester acrylique, des polymères d'acide hydroxybutyrique, des polymères d'oxalate d'alkylène, un polyorthoester, un polycarbonate et des polyaminoacides.

6. Préparation de microsphères à libération prolongée contenant un médicament antipsychotique suivant l'une quelconque des revendications 1 à 5, dans laquelle le polymère de haut poids moléculaire doué d'histocompatibilité in vivo consiste en un ou plusieurs composés choisis entre un polymère d'acide lactique, un polymère d'acide glycolique, un polymère d'acide citrique, un polymère d'acide malique et un polymère d'acide (lactique-co-glycolique).

7. Préparation de microsphères à libération prolongée contenant un médicament antipsychotique suivant l'une quelconque des revendications 1 à 6, dans laquelle le polymère de haut poids moléculaire doué d'histocompatibilité in vivo consiste en un ou plusieurs composés choisis entre un polymère d'acide lactique, un polyester d'acide glycolique, un polymère d'acide citrique, un polymère d'acide malique, un polymère d'acide (lactique-co-glycolique), un polymère d'ester-α-cyanacrylique, un polymère d'acide β-hydroxybutyrique, un polymère d'oxalate de triméthylène, un polyorthoester, un polyorthocarbonate, un polymère de carbonate d'éthylène, un polymère d'acide γ-benzyl-L-glutamique et la poly-L-alanine.

8. Préparation de microsphères à libération prolongée contenant un médicament antipsychotique suivant l'une quelconque des revendications 1 à 7, dans laquelle ledit médicament antipsychotique hydrophobe est sous forme de microcristaux ayant des dimensions moyennes de particules de 0,1 à 5 µm.

9. Préparation de microsphères à libération prolongée contenant un médicament antipsychotique suivant l'une quelconque des revendications 1 à 8, ladite préparation de microsphères à libération prolongée contenant un médicament antipsychotique consistant en une suspension aqueuse.

10. Procédé pour la production d'une préparation de microsphères à libération prolongée contenant un médicament antipsychotique, qui comprend les étapes consistant à préparer une phase huileuse comprenant un polymère de haut poids moléculaire doué d'histocompatibilité in vivo contenant un médi-

cament antipsychotique hydrophobe sous forme de microcristaux ayant des dimensions moyennes de particules égales ou inférieures à 5 µm, à ajouter la phase huileuse à une phase aqueuse, à soumettre le mélange résultant à un traitement d'émulsionnement pour obtenir une émulsion de type huile/eau, puis à éliminer le solvant présent dans la phase huileuse par un procédé d'élimination de l'eau incorporée.

11. Procédé pour la production d'une préparation de microsphères à libération prolongée contenant un médicament antipsychotique suivant la revendication 10, dans lequel ledit médicament antipsychotique hydrophobe est choisi entre l'halopéridol, le brompéridol, la fluphénazine, la chlorpromazine, le sulpiride, la carpipramine, la clocapramine, la mosapramine, la rispéridone, la clozapine, l'oranzapine et le sertindole ainsi que leurs sels d'addition d'acides pharmaceutiquement acceptables.

12. Procédé pour la production d'une préparation de microsphères à libération prolongée contenant un médicament antipsychotique suivant la revendication 10 ou 11, dans lequel ledit médicament antipsychotique hydrophobe est choisi entre l'halopéridol, le brompéridol, le maléate de fluphénazine, la chlorpromazine, le dibenzoate de chlorpromazine, le sulpiride, le chlorhydrate de carpipramine, le maléate de carpipramine, le chlorhydrate de clocapramine, le chlorhydrate de mosapramine, la rispéridone, la clozapine, l'oranzapine et le sertindole.

13. Procédé pour la production d'une préparation de microsphères à libération prolongée contenant un médicament antipsychotique suivant la revendication 10, dans lequel ledit médicament antipsychotique hydrophobe est choisi entre l'halopéridol et le brompéridol.

14. Procédé pour la production d'une préparation de microsphères à libération prolongée contenant un médicament antipsychotique suivant la revendication 10, dans lequel le polymère de haut poids moléculaire doué d'histocompatibilité in vivo consiste en un ou plusieurs composés choisis entre des polymères d'esters d'acides gras et leurs copolymères, des polymères d'ester acrylique, des polymères d'acide hydroxybutyrique, des polymères d'oxalates d'alkylène, des polyorthoesters, un polycarbonate et des polyaminoacides.

15. Procédé pour la production d'une préparation de microsphères à libération prolongée contenant un médicament antipsychotique suivant l'une quelconque des revendications 10 à 14, dans lequel le polymère de haut poids moléculaire doué d'histocompatibilité in vivo consiste en un ou plusieurs composés choisis entre un polymère d'acide lactique, un polymère d'acide glycolique, un polymère d'acide citrique, un polymère d'acide malique et un polymère d'acide (lactique-co-glycolique).

16. Procédé pour la production d'une préparation de microsphères à libération prolongée contenant un médicament antipsychotique suivant l'une quelconque des revendications 10 à 15, dans lequel le polymère de haut poids moléculaire doué d'histocompatibilité in vivo consiste en un ou plusieurs composés choisis entre un polymère d'acide lactique, un polymère d'acide glycolique, un polymère d'acide citrique, un polymère d'acide malique, un polymère d'acide (lactique-co-glycolique), un polymère d'ester α-cyanacrylique, un polymère d'acide β-hydroxybutyrique, un polymère d'oxalate de triméthylène, un polyorthoester, un polyorthocarbonate, un polymère de carbonate d'éthylène, un polymère γ-benzyl-L-glutamique et la poly-L-alanine.

17. Procédé pour la production d'une préparation de microsphères à libération prolongée contenant un médicament antipsychotique suivant l'une quelconque des revendications 10 à 16, dans lequel ledit médicament antipsychotique hydrophobe est sous forme de microcristaux ayant des dimensions moyennes de particules de 0,1 à 5 µm.

18. Procédé pour la production d'une préparation de microsphères à libération prolongée contenant un médicament antipsychotique suivant l'une quelconque des revendications 10 à 17, dans lequel un solvant de la solution de polymère de haut poids moléculaire doué d'histocompatiblité in vivo est un solvant qui a un point d'ébullition égal ou inférieur à 120°C et qui n'est pas miscible à l'eau.

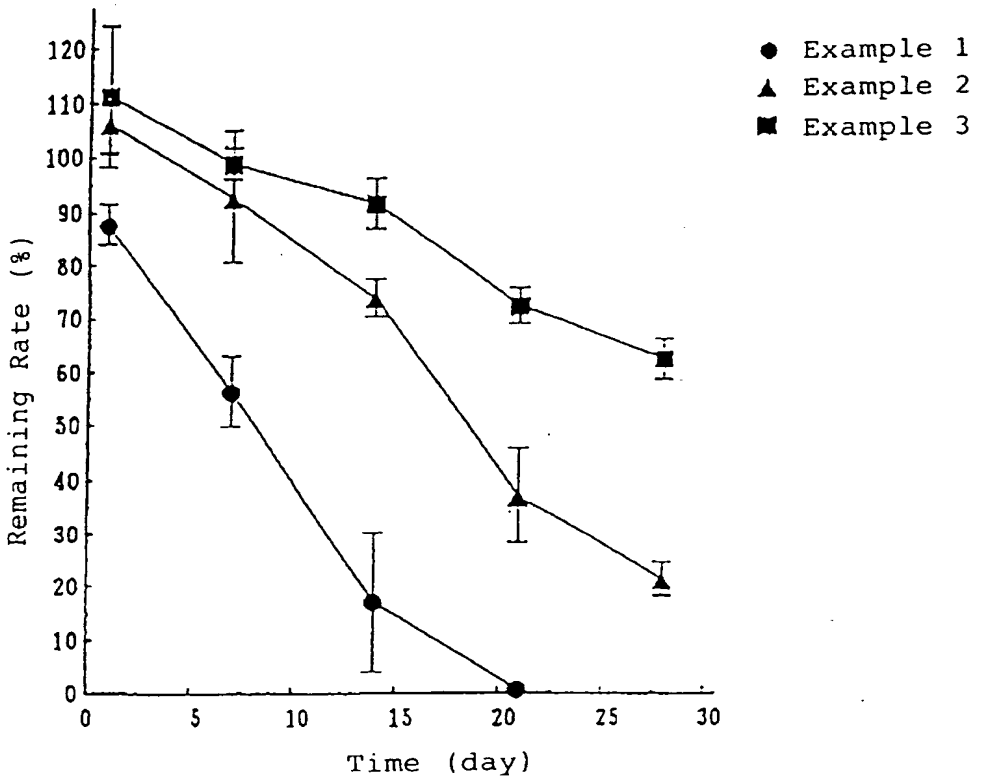
19. Procédé pour la production d'une préparation de microsphères à libération prolongée contenant un médicament antipsychotique suivant l'une quelconque des revendications 10 à 18, dans lequel un ou plusieurs composés choisis entre des surfactants anioniques, des surfactants non ioniques, la polyvinylpyrrolidone, un polymère d'alcool vinylique, la carboxyméthylcellulose, la lécithine et la gélatine sont ajoutés comme agents émulsionnants à la phase aqueuse.

20. Procédé pour la production d'une préparation de microsphères à libération prolongée contenant un médicament antipsychotique suivant l'une quelconque des revendications 10 à 19, dans lequel ladite préparation de microsphères à libération prolongée contenant un médicament antispychotique consiste en une suspension aqueuse.

21. Préparation de microsphères à libération prolongée contenant un médicament antipsychotique suivant l'une quelconque des revendications 1 à 7, dans laquelle ledit médicament antipsychotique hydrophobe est sous forme de microcristaux ayant des dimensions moyennes de particules de 0,5 à 5 µm.

22. Préparation de microsphères à libération prolongée contenant du brompéridol ou de l'halopéridol, qui est produite en incorporant du brompéridol ou de l'halopéridol sous forme de microcristaux ayant des dimensions moyennes de particules de 0,5 à 5 µm à une substance de base comprenant un polymère de haut poids moléculaire doué d'histocompatibilité in vivo.

Fig. 1


Example 1
Example 2
Example 3
Remaining Rate (%)
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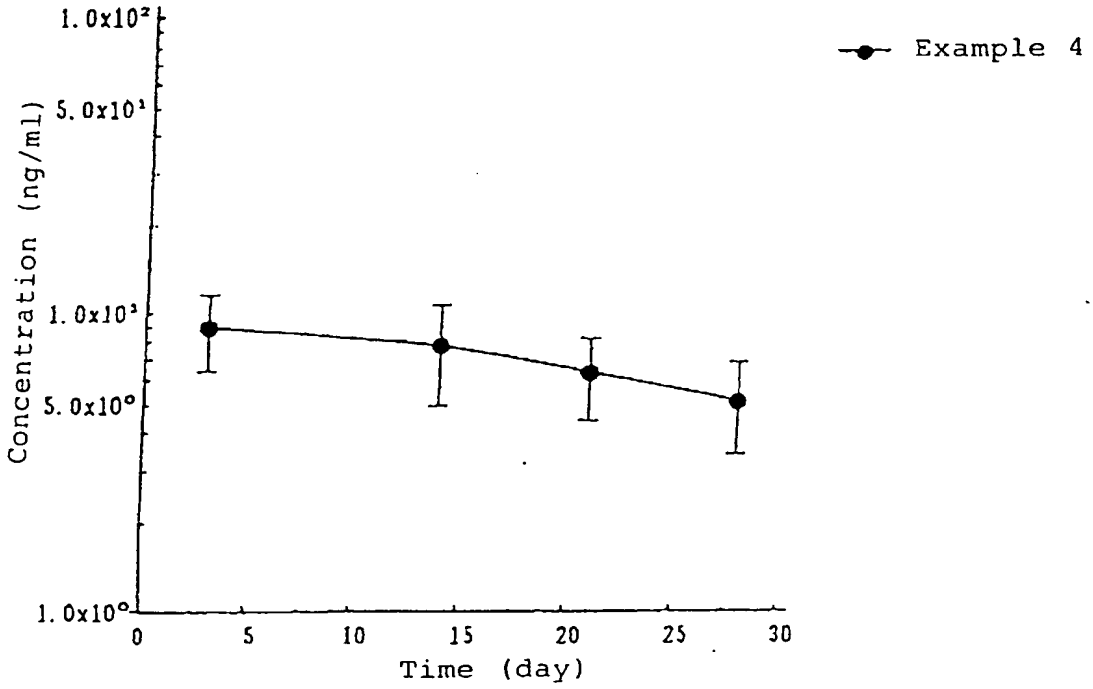
20
30
40
50
60
70
80
90
100
110
120
0
5
10
15
20
25
30

Fig. 2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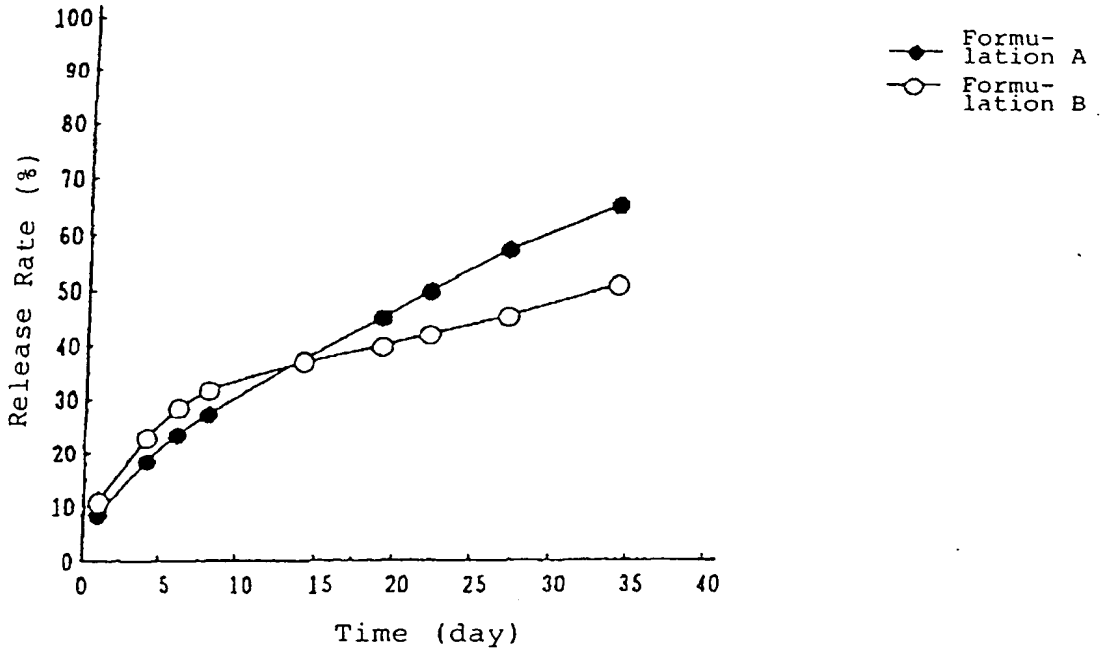
5.0x10¹
1.0x10³
5.0x10°
1.0x10°
Concentration (ng/ml)
0
5
10
15
20
25
30
Time (day)
Example 4

Fig. 3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20
25
30
35
40
Time (day)
Formu-lation A
Formu-lation B